

Final Report

3-Month Intranasal Study with Metoclopramide Nasal Spray in Cynomolgus Monkeys with a 1-Month Recovery

PREPARED FOR:
Roberts Pharmaceutical Corporation

COVANCE STUDY NUMBER:
6988-101

VOLUME:
.1 of 1



Sponsor:

Roberts Pharmaceutical Corporation
4 Industrial Way West
Eatontown, New Jersey 07724-2274

FINAL REPORT

Study Title:

3-Month Intranasal Study with Metoclopramide Nasal
Spray in Cynomolgus Monkeys with a 1-Month Recovery

Author:

Michael D. DuVall, DVM, PhD

Study Completion Date:

Performing Laboratory:

Covance Laboratories Inc.
9200 Leesburg Pike
Vienna, Virginia 22182-1699

Laboratory Study Identification:

Covance 6988-101

COMPLIANCE STATEMENT

**3-Month Intranasal Study with Metoclopramide Nasal
Spray in Cynomolgus Monkeys with a 1-Month Recovery**

This study, as performed by Covance Laboratories Inc., was conducted in compliance with the Food and Drug Administration Good Laboratory Practice Regulations as set forth in Title 21 of the United States Code of Federal Regulations Part 58, issued December 22, 1978 (effective June 20, 1979), and with any applicable amendments.



Michael D. DuVall, DVM, PhD
Study Director

Date

QUALITY ASSURANCE STATEMENT

3-Month Intranasal Study with Metoclopramide Nasal Spray in Cynomolgus Monkeys with a 1-Month Recovery

Quality Assurance inspections and reviews of this study were conducted according to the standard operating procedures of the Quality Assurance Unit and according to the Good Laboratory Practice regulations of the Food and Drug Administration Good Laboratory Practice Regulations as set forth in Title 21 of the United States Code of Federal Regulations, Part 58, issued December 22, 1978 (effective June 20, 1979) and with any applicable amendments. These inspections and reviews were performed and findings were reported to the Study Director and management as follows:

Dates of Inspection/Review	Dates Findings Reported	Inspector/Reviewer
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Protocol Review:

N. Strickland

Inspection and/or Data Review:

(Dosing)

N. Strickland

(Data)

C. Allman

(Necropsy)

N. Strickland

(Data)

N. Strickland

(Data)

N. Strickland

Report and Data Review:

(Draft)

L. Cassell

(Postaudit)

S. Godfrey

(Amendment no. 5)

G. Faist


Gerald Faist Jr.

Date Released

STUDY IDENTIFICATION

**3-Month Intranasal Study with Metoclopramide Nasal
Spray in Cynomolgus Monkeys with a 1-Month Recovery**

Test Material:	Metoclopramide Nasal Spray; 10 mL bottles with spray applicators (200 mg/mL)
Sponsor:	Roberts Pharmaceutical Corporation 4 Industrial Way West Eatontown, New Jersey 07724-2274
Study Monitor:	David Haenick, PhD
Study Location:	Covance Laboratories Inc. 9200 Leesburg Pike Vienna, Virginia 22182-1699
Study Director:	Michael D. DuVall, DVM, PhD (703) 893-5400
Study Timetable	
Study Initiation:	
In-life Start Date:	
In-life End Date:	
Study Completion Date:	

KEY PERSONNEL**3-Month Intranasal Study with Metoclopramide Nasal
Spray in Cynomolgus Monkeys with a 1-Month Recovery**

Study Director:	Michael D. DuVall, DVM, PhD
Study Toxicologist:	Sharon P. Dyke, BS
Study Coordinator:	Joy T. Palabrica, BA
Ophthalmology Examinations:	William E. Ridder, DVM, MS, PhD
Veterinarian:	William E. Ridder, DVM, MS, PhD
Clinical Pathologist:	Renée C. Pearson, MS, DVM, Diplomate, ACVP
Anatomic Pathologist:	Borge M. Ulland, DVM, Diplomate, ACVP
Biostatistician:	Ajit K. Thakur, PhD
Supervisor, Dose Formulations:	William Caparoon, AA
Supervisor, Laboratory Animal Medicine	Robert L. Ridgway, DVM, Diplomate, ACLAM
Supervisor, Large-Animal Toxicology:	Jeffery G. Linebaugh, LATg
Supervisor, Postlife and Clinical Pathology Laboratories:	Kelly Bell, BS

CONTENTS

	Page
ABSTRACT	10
PURPOSE	11
REGULATORY COMPLIANCE	11
TEST AND CONTROL MATERIALS	11
Test Material	11
Control Material	11
Reserve (Archive) Samples	12
Disposition	12
TEST ANIMALS AND HUSBANDRY	12
Environmental Enrichment and Dietary Supplements	13
Randomization	13
PROCEDURES	14
Group Designations and Dosing Protocol	14
Dose Selection Rationale	14
DOSING PROCEDURES	15
Dose Preparation	15
Method of Administration	15
Reason for Dosing Route	15
Dose Analyses	15
ANTEMORTEM PROCEDURES	16
Observation of Animals	16
Bioavailability	16
Clinical Pathology	17
POSTMORTEM PROCEDURES	18
Necropsy	18
Organ Weights	18
Bone Marrow Smears	19
Tissue Preservation	19
Histopathology	20
Statistical Analyses	20
Record Retention	21

CONTENTS (continued)

	Page
Results and Discussion	22
In-life Observations	22
Clinical Pathology	25
Anatomic Pathology	26
Toxicokinetic Analysis	26
CONCLUSIONS	27
PATHOLOGY REPORT	29
COMMENTS ON THE DATA	34
CODES, ABBREVIATIONS, AND UNITS	35
General Codes and Abbreviations	36
Codes for Clinical Pathology	38
Abbreviations for Clinical Hematology	42
Abbreviations for Clinical Chemistry	44
Abbreviations for Urine Chemistry	47
Abbreviations for Clinical Urinalysis	48
Codes for Anatomic Pathology	49
TABLES	
1A - Summary of Clinical Observations	52
1B - Summary of Ophthalmic Findings	55
2 - Nasal Irritation Scoring	56
3 - Summary of Body Weight Data	83
4A - Summary of Clinical Hematology Data	85
4B - Summary of Clinical Chemistry Data	101
5 - Plasma Drug Level Data	121
6A - Incidence of Macroscopic Observations - Terminal Sacrifice	122
6B - Incidence of Macroscopic Observations - Recovery Sacrifice	129
7A - Summary of Organ Weight Data - Terminal Sacrifice	136
7B - Summary of Organ Weight Data - Recovery Sacrifice	148
8A - Incidence of Microscopic Observations - Terminal Sacrifice	160
8B - Incidence of Microscopic Observations - Recovery Sacrifice	166

CONTENTS (continued)

	Page
FIGURES	
Figure 1	175
Figure 2	176
Figure 3	177
Figure 4	178
 APPENDIX 1	
Protocol	180
Protocol Amendment No. 1	196
Protocol Amendment No. 2	197
Protocol Amendment No. 3	198
Protocol Amendment No. 4	200
Protocol Amendment No. 5	202
Protocol Deviations	204
 APPENDIX 2	
Individual Clinical Observations	206
Individual Animal Fate Data	271
 APPENDIX 3	
Individual Body Weight Data	273
 APPENDIX 4	
Individual Clinical Hematology Values	278
Individual Clinical Chemistry Values	304
 APPENDIX 5	
Individual Anatomic Pathology Data	325

CONTENTS (continued)

Page

APPENDIX 6	
Toxicokinetic Report	370
 APPENDIX 7	
Final Analytical Report	391

ABSTRACT

The purpose of the study was to evaluate the toxicity and bioavailability of Metoclopramide Nasal Spray when administered by intranasal spray to cynomolgus monkeys for at least 13 weeks and to assess the reversibility of any effects after a 4-week recovery period.

Male and female cynomolgus monkeys were assigned to four groups (six/sex/group in Groups 1 and 4 and three/sex/group in Groups 2 and 3). Three monkeys/sex in Groups 1 and 4 were designated for recovery. Each group received dose preparations four times daily containing the control material or metoclopramide at a dose level of 40, 80, or 160 mg/animal/day.

Criteria evaluated during the study included survival, clinical observations, nasal irritation, body weights, ophthalmic examinations, clinical pathology, gross pathology, organ weights, and histopathology. Blood samples were analyzed to determine plasma levels of metoclopramide.

Four-times-daily administration of Metoclopramide Nasal Spray at dosages of 40, 80, and 160 mg/animal/day produced behavioral effects that were consistent with the known pharmacologic side-effects of metoclopramide: hypoactivity, somnolence, hyperactivity (increased stereotypical behaviors), and dissociative posturing. Their incidence and severity were dose-dependent and were most prevalent during Weeks 1-3. The 40 and 160 mg/animal/day females tended to have a greater incidence of hypoactivity than the males in these groups. In addition, all of the 160 mg/animal/day females exhibited intention tremors, whereas only four males in this group were affected. The erythrocyte mass was decreased in the males treated at the 160 mg/animal/day level. The latter findings suggested a gender difference in the effects of metoclopramide at the highest dosage evaluated.

In conclusion, pharmacologic effects were observed at all dose levels and a no-observable-effect level (NOEL) was not determined. Due to the severity and incidence of the hypoactivity and tremors among the females treated with 80 mg/animal/day and the males treated with 160 mg/animal/day, the no-observable-adverse-effect level (NOAEL) was determined to be 40 and 80 mg/animal/day in the females and males, respectively.

PURPOSE

This study was designed to evaluate the toxicity and bioavailability of Metoclopramide Nasal Spray when administered by intranasal spray four times daily to cynomolgus monkeys for at least 3 months and to assess the reversibility of any effects after a 4-week recovery period.

REGULATORY COMPLIANCE

The study, as performed by Covance, was conducted in compliance with the Food and Drug Administration Good Laboratory Practice Regulations as set forth in Title 21 of the United States Code of Federal Regulations, Part 58, issued December 22, 1978 (effective June 20, 1979), and with any applicable amendments.

The protocol was reviewed and approved by the Institutional Animal Care and Use Committee at Covance.

TEST AND CONTROL MATERIALS

Test Material

The test material, Metoclopramide Nasal Spray, Lot No. R980104, was received from Roberts Pharmaceutical Corporation, Ontario, Canada, on _____ and stored at room temperature, protected from light. It was described as a clear, colorless liquid. Information on purity, stability, synthesis methods, composition, or other characteristics that define the test material is on file with the Sponsor.

Control Material

The control material, 0.9% sodium chloride injection, USP, Lot No. 46-165-DK, was received from Roberts Pharmaceutical Corporation, Ontario, Canada, on _____ and was stored at room temperature. It was described as a clear, colorless liquid. Information on synthesis methods, composition, or other characteristics that define the